Cancer

There has been more work done on genes that predispose to cancer than on genes associated with any other group of diseases. Molecular biology is useful for other areas of cancer research as well. For instance, molecular markers can improve the quality of epidemiology studies by clarifying disease subgroups. By identifying homogeneous subgroups of disease, stronger associations can be found with the underlying risk factors. Dale Sandler, chief of the Environmental and Molecular Epidemiology Section, has recently completed a study of acute leukemia that demonstrates this principle. Acute leukemias are a mixed group of cancers with diverse causes. Sandler interviewed a large sample of patients and healthy comparison persons about their jobs, hobbies, and medical history. Leukemia patients were classified not only according to clinically important pathologic subtypes, but also by chromosome abnormalities of the blood-forming tissues and by whether or not there was a mutation of the *ras* oncogene. (Specific *ras* gene mutations have been seen with chemical exposures in animal studies.)

Results on smoking show the usefulness of better classification of patients. Smoking was found to be associated in older patients with a twofold increase in risk for acute myeloid leukemia and a threefold risk for acute lymphocytic leukemia. This relation with smoking was even stronger within certain subtypes of leukemia, which may offer clues as to how smoking causes the disease. For example, Sandler has found that smoking is more common among patients with loss of part or all of chromosome 7. Deletion of this chromosome has previously been seen in patients with a history of chemotherapy for other diseases and in patients with occupational exposure to solvents. This suggests that the leukemogenic effect of smoking may be due to chemicals found in cigarette smoke (e.g., benzene).

Similarly, Sandler and her colleagues have found that occupational exposure to solvents is strongly related to mutation of the *ras* oncogene. In this case, the occupational exposure had not been associated with the overall risk of leukemia.

Oncogenes and their relation to environmental exposures are being explored by Jack Taylor, senior clinical investigator. There are at least two classes of genes—oncogenes and tumor-suppressor genes—that seem to be critical targets for environmental agents in cancer initiation and progression. Taylor's strategy is to collect tumors from people with high exposures to known environmental carcinogens and then to look for evidence of damage to specific gene sequences. Taylor has set up collaborations with groups from the United States, Norway, and Canada to collect tumors from persons with unique exposures. The majority of his work has been on lung and bladder cancer, both of which have strong environmental determinants. Taylor has collected bladder tumors from persons exposed to benzidine, β-naphthylamine, cyclophosphamide, and cigarette smoke and is pursuing samples from persons exposed to arsenic, polycyclic aromatic hydrocarbons, and phenacetin. He has collected lung tumors from persons exposed to radon, nickel, asbestos, and cigarette smoke, and is planning projects to collect tumors from people exposed to arsenic and chromium.

Senior staff. (Left to right) Jack Taylor, Dale Sandler, Allen Wilcox, and Freja Kamel.

Many of these samples come from blocks of tissue preserved by pathologists after surgery. Even specimens that are 30 years old or more, retrieved from remote recesses of hospital basements, can provide ample DNA from a single microtome slice of tissue. Using the polymerase chain reaction (PCR) technique, specific genes can be screened and sequenced. By contrasting the pattern of mutations in tumors from people with different exposures, the critical chain of events that lead to environmentally induced cancers can begin to be characterized.

The epidemiologic use of laboratory methods is not new. Today, however, the range of laboratory tools relevant to epidemiology goes far beyond infectious diseases. Epidemiologic projects at NIEHS reflect the spectrum of laboratory methods, from measurement of body burden of toxins to the application of genetic assays, that clarify and strengthen the study of environmental hazards and their effects on human health.

Vision for the Future Sets NIEHS Priorities

"At a time when expanding research opportunities are at odds with tighter budgets, priority setting is a must," says Kenneth Olden, NIEHS director. Two documents will play a key role in priority setting for NIEHS: a recently completed document, NIEHS's *Vision for the Future,* and its companion report which provides the basis for the *Vision* document, the 1992 Report of the Fourth Task Force for Research Planning in Environmental Health Sciences, *Human Health and the Environment: Some Research Needs.*

The National Advisory Environmental Health Sciences Council, a key NIEHS advisory body of scientists and other professionals from outside government, oversaw the development and review of both reports. The task force report was mandated by Congress and prepared by 19 internationally recognized science and public health professionals, co-chaired by Morton Lippmann and Arthur Upton, the deputy director and former director of the Institute of Environmental Medicine, New York University Medical Center, respectively.

The NIEHS's *Vision for the Future* built on the task force report and on input over the past two years from university-based centers and scientists in the field of environmental health sciences, relevant scientific societies, colleagues at NIH and at other federal agencies, industry, and the public.

Vision for the Future describes the NIEHS mission this way:

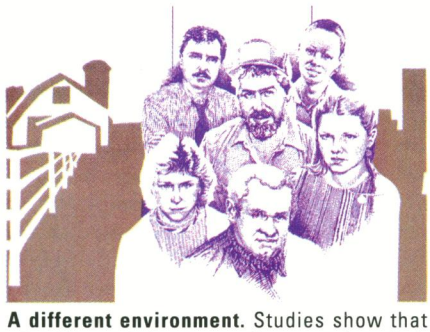
> Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of the National

Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach.

One major theme in the document is good science for good decisions. "Environmental health policy is only as good as the scientific foundation upon which it rests," states the report. NIEHS must maximize the effectiveness of public policy decisions by providing the most complete information on the environmental components of human disease and the biological mechanisms of these diseases. The institute is interested in promoting clinical research programs that can more readily translate laboratory findings into practical human therapies.

More than identifying environmental causes of diseases, NIEHS seeks to understand the molecular and genetic basis of environmentally related disorders, relying on recent advances in molecular biological techniques that enable scientists to understand the interaction of environmental agents and basic cellular functions. Promising areas for such advances include environmental effects on cell proliferation and apoptosis, events controlling differentiation and development, receptor-mediated pathobiology, and genetic susceptibility and predisposition to environmentally related diseases.

Vision for the Future sets out the institute's approach to prevention of and intervention in environmentally related disease and dysfunction. In hazard identification and characterization, NIEHS proposes to use approaches including mechanistic data, biomarkers, noncancer endpoints, development of animal model systems, and sentinel animals.



A different environment. Studies show that minorities and the poor suffer more than their share from pollution.

The report acknowledges the institute's role in providing a science base for social policy, especially in the areas of environmental justice, global climate change, and bioethics related to emerging science and technology. *Vision for the Future* also describes the institute's considerable role as an educational institution, promoting the education of science professionals in the multidisciplinary studies that are vital to environmental health sciences.

Communication is central to NIEHS's mission. Community outreach is vital to addressing environmental concerns that frequently occur in localized areas. The institute actively seeks to transfer technology developed in its laboratories to clinical and other applied use. Workshops, symposia, and conferences supported and hosted by NIEHS, often in collaboration with other organizations, are another major forum for communication.

To obtain a copy of *Vision for the Future* or the task force report, *Human Health and the Environment: Some Research Needs,* write, phone, or FAX the NIEHS Office of Communications, MD B2-05, PO Box 12233, Research Triangle Park, NC 27709; telephone (919) 541-3345, FAX (919) 541-0462.

Applications for Grants on EMF Effects Requested

People from all walks of life and of all ages are exposed to power frequency (60 Hz) electric and magnetic fields. Increasingly, scientists, regulators, and the public are asking whether human exposure to these fields involves risks to human health. NIEHS proposes to respond to these concerns by issuing two requests for grant applications (RFAs) on biological effects of electromagnetic fields (EMF).

Examples of research areas of interest under one RFA are the *in vivo* effects of EMF on melatonin; effects on reproduction and development; effects on the neuroendocrine system; effects on behavior, and effects on tumor promotion or other aspects of cancer development. Investigators are encouraged to study these or other topics that have been reported in the peer-reviewed literature.

In addition, the RFA notes that the effects of EMF on the behavior of cells exposed to electric and/or magnetic fields *in vitro* have often been cited. For example, there have been reports of EMF effects on cell membranes, RNA transcription, ornithine decarboxylase activity, calcium-ion efflux, and cellular response to hormones. Examples of research interests under this RFA include effects on calcium and calcium-mediated processes; effects on gene expression, particularly genes that may be involved in cancer; effects on signal transduction; effects on proto-oncogenes such as c-*myc*, c-*jun*, and c-*fos* in human cells; and effects on activity of protein kinase. Applications may be in any area previously reported in peer reviewed literature.

To ask questions or to receive a copy of the RFA, contact NIEHS either by FAX at 919-541-2843 or voice mail at 919-541-3319 or write to Michael J. Galvin, Jr., program administrator, Environmental Health Resources Branch, Division of Extramural Research and Training.

Environment–Breast Cancer Link and Community Outreach Targeted

The National Advisory Environmental Health Sciences Council, a key advisory body of NIEHS made up of outside science and public health professionals, has given approval for the institute to request research grant applications in two high priority areas: the determination of a possible link between environmental agents and breast cancer and the role that socioeconomic disadvantage might play in environmentally related disease and dysfunction (environmental justice). Requests for applications (RFAs) will be published in the *Federal Register*, the *NIH Guide to Grants and Contracts,* and the *Commerce Business Daily.*

The RFA on environmental agents and breast cancer will focus on the critical timing of environmental exposures and their relationship to changes in the growth and development of the mammary gland. Critical periods of time include the fetal period, birth to puberty, puberty, puberty to first pregnancy, pregancy, lactation, surgical and natural menopause, and postmenopause. Other critical periods of time may also be identified and should be studied in relation to cancer development and latency.

Exposures to chemicals or other agents that may act as environmental estrogens and influence the endogenous levels of all relevant steroid hormones are of interest. Research that explores the biologic mechanism of these environmental effects on cell growth and development and hormone synthesis and regulation will help researchers to better understand the role of these agents. Cellular processes that may be involved include cell proliferation, apoptosis, ovarian and pituitary steriod metabolism and bioavailability, growth factor regulation, ductal morphogenesis, and mammary gland cell differentiation. Research is encouraged using animal model systems, human cell lines, and tumor and normal breast tissue samples from animals or humans. For further information contact Gwen W. Collman, program administrator, NIEHS, (919) 541-4980, FAX (919) 541-2843.